SUMMARY OF CLAIMS

Claims 1, 2, 5-12, 14-26 and 37-57 are pending. Reconsideration is respectfully requested in light of the following remarks.

Claims 27-36 are canceled as being drawn toward a non-elected invention.

Claims 3, 4 and 13 are canceled.

Claims 54-59 are new.

No new matter is entered by the amendments.

Support for the new claims can be found, for example, as listed below:

Amended/New Claim #	**Support**
54-57	Fig. 8 specification page 17, line 25 – page 18, line 7; page 18, lines 18-23
58 and 59	Specification page 22, lines 30-32; page 21, lines 15-21

REMARKS

Claim Rejections – 35 USC § 112

The Examiner has rejected claims 1, 2, 5-12, 14-26 and 37-53 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for allegedly containing new matter. Specifically, the Examiner contends that while the specification appears to support a limitation drawn to a pneumatically actuated valve, the limitation reciting "one pneumatically actuated diaphragm pump" is not supported.

Applicants respectfully traverse this rejection. Support for a pneumatically actuated diaphragm pump is found throughout the specification. See, e.g., page 8, lines 29-32, where it is explained that "controlling valves in this manner allows massively parallel pneumatic actuation of a monolithic membrane for operating valves, **pumps**, reservoirs, routers, and other fluid control structures within the device." See, also, Figures 2A and 2B, which are diagrammatic representations of a pneumatically actuated diaphragm pump 210. As described in the specification at page 9, lines 1-29, the three diaphragm valves 201, 203 and 205 are placed in series and form diaphragm pump 210. These valves and the pump are pneumatically actuated. See, page 9, lines 21-23.

From this and other description throughout the specification, one of skill in the art would clearly understand that the inventors had possession of the claimed invention. Applicants respectfully request that the Examiner withdraw this rejection.

Claim Rejections – 35 USC § 103

The Examiner has rejected claims 1, 2, 5-12, 14-26, and 37-53 under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. (U.S. Patent 5,922,591; "Anderson" hereinafter) in view of Waller et al. (Applied Environmental Microbiology, 2000, vol. 66, no. 9, pages 4115-4118; "Waller" hereinafter).

Applicants claims relate to a microfluidic device having an immunocapture chamber and a DNA analysis chamber integrated on the microfluidic device. A pneumatically actuated pump is also integrated on the device and configured to pump fluid from the immunocapture chamber into the DNA analysis chamber. The immunocapture chamber is "operable to capture a target provided to the immunocapture chamber through a microfluidic channel."

Applicants' invention is able to provide effective mixing of antibody and antigen in a microfluidic device, which is required to achieve efficient immunocapture, as well as deliver the captured target to the DNA analysis chamber. This is done in microfluidic chambers, in which

processes that rely on turbulent flow to achieve said mixing (rotational mixing, shaking, inverting, vortexing, etc.) do not work due to the low Reynolds number regime. For at least these reasons, immunocapture processes performed at the macroscopic level in tubes cannot be extrapolated to microfluidic devices. Prior to Applicants' invention, the inability to transform macroscopic immunocapture processes to micron scale microfluidic devices was a barrier for the application of microfluidic systems to trace pathogen detection.

In one embodiment, the invention provides magnetic particles comprising the immunocapture material that forms a packed bed or plug in the chamber. The particles are immobilized in the chamber, e.g., by magnets. Analyte flowing through the bed allows contact between the immunocapture mechanism and the target, allowing effective capture and immobilization of the capture target within the chamber. After capture is complete, the target is released from the capture chamber to be flowed into the DNA chamber for analysis.

Anderson

Anderson describes a miniaturized integrated nucleic acid diagnostic device, which has a number of reaction, storage or analytical chambers disposed within a single unit. While Anderson describes storage chambers and PCR amplification chambers, Anderson does not teach or suggest an immunocapture chamber, or a chamber operable to capture an immunocapture target. Anderson does not teach how to constrain immunocapture particles effectively within a chamber nor does Anderson indicate how to flow an analyte solution through this bed of particles to achieve efficient capture. None of the chambers described in Anderson would be operable to capture a target on beads constrained within a chamber or to deliver the captured target to the PCR chamber.

Waller

Waller describes an immunocapture PCR assay for detection of bacterial pathogens. To isolate the target bacteria, an antibody is added to the sample containing the target, which is presumably held in a tube or other similar macroscopic (mL-sized) container. The solution is rotated to mix the two fluids and form antigen-antibody complexes. Beads are then added to the suspension, and the sample is rotated to mix the fluid sample with the beads and bind the complexes to the beads. Note that neither of these two mixing processes can be performed in microfluidic channels because of the fundamentally different Reynolds numbers involved. The beads with bound complexes are then washed to isolate the beads from the mixture. To release the genomic DNA of the bacteria, the captured cells are lysed by vortexing. After the lysis is

completed, the lysate is centrifuged. A small amount of supernatant is then ready to be amplified via PCR.

The operations described in Waller to capture the genomic DNA of the pathogen – rotational mixing, vortexing and centrifuging – require fluid physics that are not present in the low Reynolds number regime of micrometer scale chambers, and so are not operable in microfabricated chambers. This process can thus not be combined with previous microfluidic structures to achieve the desired operation.

Claims 1, 2, 5-12, 14-26, and 37-53

In rejecting these claims the Examiner states that Anderson does not describe an immunocapture chamber on its device, but that "[g]iven the motivation provided for by Waller et al., which allows one of ordinary skill in the art to detect pathogens in a sample, wherein the artisans explicitly disclose the uses of antibody and bead assisted immunocapture of pathogens, followed by the lysis of the captured pathogens prior to amplification, one of ordinary skill in the art would have had a reasonable expectation of success at creating a chamber or chambers prior to the PCR-CE detection microfluidic device of Anderson et al."

Applicants traverse this rejection at least because 1) the combination of Anderson and Waller does not result in "an immunocapture chamber integrated on a microfluidic device, the immunocapture chamber operable to capture a target provided to the immunocapture chamber through a microfluidic channel," 2) one of skill in the art at the time the invention was made would not have been motivated to combine the references, and 3) one of skill in the art at the time the invention was made would not have had a reasonable expectation of success at combining the references to arrive at the claimed invention.

First, a literal combination of the elements of Waller and Anderson does not produce a device that might reasonably be expected to function as contemplated by the specification, that is, to capture analyte in the immunocapture chamber and transport the analyte to the DNA analysis chamber. Waller shows capture of the analyte by mixing immunocapture beads with a sample containing the analyte, mixing by rotation, vortexing and centrifugation to separate the target from the rest of the sample. This will not work on a microfluidic device as claimed. Rotating the sample as in Waller will not result in proper mixing because in a microfluidic device the Reynolds number is low, preventing turbulent flow. The lack of turbulence will result in insufficient contact between the sample and the surfaces of the capture mechanism. Similarly, vortexing requires turbulent flow, and so cannot be performed on a microfluidic device. Nor does Anderson provide any teaching that would enable one of skill in the art to implement the

immunocapture method described in Waller in a microfluidic device. In particular, Anderson does not show any method of capturing a target on beads in a microfluidic chamber. Nor does Anderson show a method of releasing the target after capture in the chamber for transmission to the PCR chamber.

Second, the references do not provide unambiguous motivation to include an immunocapture mechanism on a microfluidic device. There is no suggestion in Waller of putting the immunocapture chamber on a microdevice. Nor is there any suggestion in Anderson that one of the chambers should, or even could, be used for immunocapture.

Even if there were such motivation, there was, again, no reasonable expectation of success in making it work. The inventors had to overcome several technical problems to allow proper capture and transmission of the analyte into the DNA analysis chamber. These included (1) providing proper contact between the sample containing the analyte and the immunocapture mechanism to allow effective capture of the target and (2) mechanisms for transferring the captured target from the immunocapture chamber into the DNA chamber. Before applicants' invention, these problems were not recognized or solved. The inventors provided various technical solutions to these problems, including, in one embodiment, particles comprising the immunocapture material that are immobilized to form a plug in the chamber and can capture the target. In another embodiment, Applicants provided integrated heaters to release the target from the immunocapture chamber for transport to the DNA analysis chamber.

A literal combination of the elements of Anderson and Waller would not result in immunocapture because there would be no effective mixing of the sample solution with the immunocapture beads, and therefore, would not function as an immunocapture chamber of the claimed invention. Even if one were motivated to perform immunocapture on chip, there was no teaching of how to successfully accomplish this with good mixing and high capture efficiency. Applicants found solutions to these problems and, therefore, their invention was not obvious.

For at least these reasons, Applicants submit that independent claims 1, 8, 11 and 37 and their dependent claims are patentable. Applicants also submit various dependent claims are independently patentable. For example, claim 26 recites "fluidics layer and a pneumatic layer [that] sandwich [a] membrane layer, wherein the pneumatic layer comprises pneumatic channels that actuate the diaphragm pumps using vacuum or pressure." In rejecting this claim, the Examiner pointed only to col. 29, lines 54-57 of Anderson, which states that the valves in Figure 12 may be controlled pneumatically. However, examination of Anderson shows that it does not disclose any pneumatic channels, but rather an inlet port 1278 and vent port 1270. The only channels described in Anderson are fluidic channels.

Double Patenting

Claims 1-26 and 38-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-39 of copending Application No. 10/750,533. Applicants traverse.

The rejection is acknowledged and will be addressed upon a finding of otherwise allowable subject matter.

Conclusion

If prosecution of this application can be assisted by telephone, the Examiner is requested to call Applicant's undersigned attorney at (510) 663-1100.

If any fees are due in connection with the filing of this amendment (including any fees due for an extension of time), such fees may be charged to Deposit Account No. 504480 (Order No. UCALP031).

Dated: July 22, 2008

Respectfully submitted,
Weaver Austin Villeneuve & Sampson LLP

/Denise S. Bergin/

Denise Bergin
Reg. No. 50,581

P.O. Box 70250
Oakland, CA 94612-0250